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WO 02/07731 A2

(54) Title: COMPOSITION FOR TREATMENT OF OCULAR HYPERTENSION AND GLAUCOMA

(57) Abstract: 15-keto prostaglandin compounds containing a ring structure at the end of the omega chain are used as ocular applied intraocular pressure reducing agents. They are applied in a dose below the known dose for the corresponding 15-OH compound.

at a dosage of one drop, or about 30 µl, providing 1.5 µg per dose. Latanoprost is named by Stjernschantz as 13, 14-dihydro-17-phenyl-18, 19,20-trinor-$PGF_2\alpha$ isopropyl ester.

Another compound of this family known to date is 13,14-dihydro-15-oxo-17-phenyl- 18,19,20-trinor $PGF_2\alpha$ isopropyl ester, hereinafter referred to as 15-keto latanoprost.

The above noted patent describes a wide potential dosage range as therapeutically active. For example, see column 5, lines 33-66 of the '128 patent ("The composition contains about 0.1-30 µg, especially 1-10 µg, per application of the active substance . . .") Even so, the lowest dosage used in the '128 patent for any test compound for evaluating IOP reduction in humans or monkeys is 1.0 µg per eye. For 15-keto latanoprost in the '128 patent, the tested dosage in healthy human volunteers is 5 µg per eye and is 3 µg in the monkey eye. Latanoprost is tested in the '128 patent at a dosage of 1.0 µg per eye in healthy human volunteers and at a dosage of 10.4 µg in the monkey eye.

Latanoprost at its clinical concentration can cause pigmentation of the iris, a mild IOP spike and/or mild hyperemia.

SUMMARY OF THE INVENTION

effective dose of the corresponding 15-OH compound.

In another aspect, the present invention relates to an ophthalmic composition for maintaining a reduced intraocular pressure in a mammal by periodically administrating the same to the mammal, which comprises an effective amount of a 15-keto prostaglandin compound containing a ring structure at the end of the omega chain.

In another aspect, the present application also relates to use of a 15-keto prostaglandin compound containing a ring structure at the end of the omega chain for manufacturing the above described ophthalmic composition.

DESCRIPTION OF THE DRAWING

Figures 1 and 2 set forth the results of Example 1 comparing the employment of a dose of 0.175 μg latanoprost (Fig. 1) and the same dose of 15-keto latanoprost (Fig 2) in the monkey eye.

Figure 1 shows effect of 0.0005% latanoprost on intraocular pressure (IOP) in monkeys. Latanoprost was instilled into the right eye. The left eye received the vehicle. No significant difference between the latanoprost-treated eye and the vehicle treated contralateral eye (Student's t-test)

Figure 2 shows effect of 0.0005% 15-keto-latanoprost on intraocular pressure (IOP) in monkeys. 15-keto-latanoprost was instilled into the right eye. The left eye

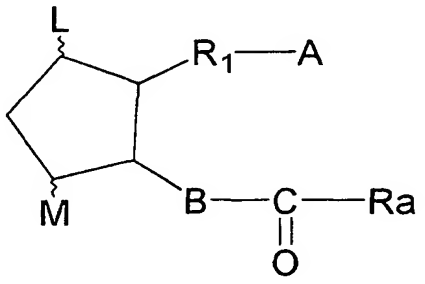
alone.

##p<0.01 as compared with 0.005% latanoprost + 0.0005% latanoprost (Turkey's comparison)

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the employment of varying, including small, ocular dosages of a 15-keto prostaglandin compound containing a ring structure at the end of the omega chain as an IOP reducing agent, administered topically to the eye in the treatment of glaucoma or ocular hypertension.

The preferred 15-keto prostaglandin compound of the present invention is represented by the formula (I),



(I)

wherein L and M are hydrogen atom, hydroxy, halogen atom, lower alkyl, lower alkoxy, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-CH_2OH$, $-COCH_2OH$, $-COOH$ or a functional derivative thereof;

B is $-CH_2-CH_2-$, $-CH=CH-$ or $-C\equiv C-$;

The term "lower" throughout the specification is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term "lower alkyl" refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

The term "lower alkoxy" refers to a group of lower alkyl-O-, wherein lower alkyl is as defined above.

The term "hydroxy(lower)alkyl" refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl.

The term "lower alkanoyloxy" refers to a group represented by the formula RCO-O-, wherein RCO- is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term "cyclo(lower)alkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cyclo(lower)alkyloxy" refers to the group of cyclo(lower)alkyl-O-, wherein cyclo(lower)alkyl is as defined above.

are as described above.

The term "heterocyclic-oxy group" means a group represented by the formula HcO-, wherein Hc is a heterocyclic group as described above.

The term "functional derivative" of A includes salts (preferably pharmaceutically acceptable salts), ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include conventionally used non-toxic salts, for example a salt with an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt (such as methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)ethane salt, monomethyl-monoethanolamine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl

phenyl ester, tosyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

The amides of A mean a group represented by the formula -CONR'R", wherein each of R' and R" is hydrogen atom, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl and lower alkynyl, and include for example lower alkyl amides such as methylamide, ethylamide, dimethylamide and diethylamide; arylamides such as anilide and toluidide; and alkyl- or aryl-sulfonylamides such as methylsulfonylamide, ethylsulfonyl-amide and tolylsulfonylamide.

Preferred examples of L and M include hydroxy and oxo, and especially, M and L are hydroxy to provide a 5-membered ring structure of, so called, PGF type.

Preferred A is $-COOH$, $-CH_2OH$, or its pharmaceutically acceptable salt, ester, ether or amide thereof.

Preferred R_1 is an unsubstituted saturated or unsaturated bivalent lower-medium aliphatic hydrocarbon residue. It may preferably have 1-10 carbon atoms, more preferably, 2-8 carbon atoms.

Examples of R_1 include, for example, the following

$-CH_2-CH_2-$,

having a primary type configuration and a compound of a non-primary type configuration.

When a 15-keto-PG compound of the present invention has for example a single bond between carbon atom number 13 and 14, the compound may be in the keto-hemiacetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and oxo at position 15.

If such tautomeric isomers as above are present, the proportion of both tautomeric isomers varies with the structure of the rest of the molecule or the kind of the substituent present. Sometimes one isomer may predominantly be present in comparison with the other. However, it is to be appreciated that the compounds used in the invention include both isomers. Further, while the compounds used in the invention may be represented by a structure formula or name based on keto-type regardless of the presence or absence of the isomers, it is to be noted that such structure or name does not intend to exclude the hemiacetal type compound.

The present invention includes any of the isomers such as the individual tautomeric isomers, a mixture thereof, or the optical isomers, a mixture thereof, a racemic mixture, and other steric isomers useful for the same purpose.

In the method of the present invention, the above-described compounds are topically administered to the

compound causes substantially no or less side effects including iridic pigmentation, an initial IOP spike and any hyperemia than those of the corresponding 15-OH compound. Accordingly, in the embodiment where the ophthalmic composition of the present invention is to be used for reducing IOP or for treating glaucoma in a mammal, the composition contains the 15-keto prostaglandin compound in an amount which provides a dose of the 15-keto prostaglandin compound below the therapeutically effective dose of the corresponding 15-OH compound.

As noted above, the clinical dose for latanoprost is about 1.5 μg per eye. At one-tenth the clinical dose, latanoprost is essentially inactive. Quite surprisingly, 15-keto latanoprost is an effective IOP reducing agent when used at about one-tenth the clinical dose of latanoprost. It is contemplated in one embodiment of the present invention that the dosage range for 15-keto latanoprost as a topically applied ocular IOP reducing agent is about 0.05 to 0.75 μg/eye, preferably about 0.075 to 0.25 μg/eye, more preferably about 0.1 to 0.175 μg/eye. In another embodiment of the present invention, the dosage range for 15-keto latanoprost as a topically applied ocular IOP reducing agent is about 0.05 to below 5.0 μg/eye, or about 0.1 to 4.5 μg/eye, or about 0.5 to 2.5 μg/eye, or about 1.0 to 2.0 μg/eye.

μg/eye, preferably about 0.075 to 0.25 μg/eye, more preferably about 0.1 to 0.175 μg/eye.

Another family of 15-keto prostaglandin compounds which should be useful in the practice of the present invention are 15-oxo-17-phenyl-18,19,20-trinor $PGF_2\alpha$ N-ethylamide and 13,14-dihydro-15-oxo-17-phenyl-18,19,20-trinor $PGF_2\alpha$ N-ethylamide. The low dosage contemplated herein for these compounds is below 15 μg/eye to as low as 0.05 μg/eye. In another embodiment of this invention, these two compounds are topically applied to the eye in a dosage of about 10μg to 0.1 μg/eye, or about 8μg to 0.5μg/eye, or about 6μg to 1 μg/eye. See U.S. 5,352,708 and U.S. 6,037,364 for the corresponding 15-OH compound, 17-phenyl-18,19,20 trinor $PGF_2\alpha$ N-ethylamide, which has a clinical (daily) dose (FDA approved dose) of one drop of a 0.030% solution. As of this writing the clinical dosage of this compound is not known by the applicant; however, with typical drop sizes of about 20 to 50 μl, most usually about 30 to 35 μl, the dosage is estimated at about 6 to 15 μg/eye, probably about 9 μg/eye.

In the embodiment where the ophthalmic composition of the present invention is to be used for maintaining a reduced intraocular pressure in a mammal, the dose of the 15-keto compound is not limited. The dose of the 15-keto prostaglandin compound in this embodiment may be

The intraocular pressure lowering effects of the 0.0005% solution of 13,14-dihydro-15-keto-17-phenyl-18, 19,20-trinor-$PGF_2\alpha$-isopropyl ester (15-keto-latanoprost) and the 0.0005% solution of 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester (latanoprost) were compared following a single, topical ocular instillation in monkeys.

No intraocular pressure lowering effect was noted following the instillation of 0.0005% latanoprost. On the other hand, the instillation of 0.0005% 15-keto-latanoprost lowered the intraocular pressure by 2.4 mmHg 8 hours after the administration as compared with the pre-treatment value. . The reduction in the intraocular pressure by the instillation of 15-keto-latanoprost was statistically significant as compared with that by the instillation of the vehicle (contralateral eye) or of 0.0005% latanoprost.

These results indicate that 15-keto-latanoprost exerts a potent intraocular pressure lowering effect with a minute dose, and suggest that 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor- $PGF_2\alpha$ (15-keto acid of latanoprost) itself produced as a metabolite from latanoprost in the eyes participates in the reduction in the intraocular pressure after the instillation of latanoprost.

Materials and Methods

1. Test substance

Group	Administration method	Volume of administration	n
15-keto-latanoprost 0.0005%	Instillation	35 µL/eye	5
Latanoprost 0.0005%	Instillation	35 µL/eye	5

Five monkeys were divided into 2 groups of the group 1 (3 monkeys) and group 2 (2 monkeys). The 0.0005% 15-keto-latanoprost and 0.0005% latanoprost were instilled into the right eye of monkeys in the group 1 and 2, respectively. One week later, 0.0005% latanoprost and 0.0005% 15-keto-latanoprost were instilled into the right eye of monkeys in the group 1 and 2, respectively, in a crossover way. Thirty-five µL of each test solution was administered by use of a micropipet (Pipetman P 100, Gilson). To the left eye the same volume of the vehicle was administered. The intraocular pressure in each group before the instillation was as follows (in mmHg, mean ± S.E.): the group receiving 15-keto-latanoprost; the right eye: 16.6 ± 0.5, the left eye: 16.6 ± 0.2, the group receiving latanoprost; the right eye: 15.8 ± 0.7, the left eye: 17.0 ± 0.3. There were no statistically significant differences between the values of the intraocular pressure before the instillation (Student's t-test).

5. Measurement of intraocular pressure

The animals were systemically anesthetized by an

keto-latanoprost was also statistically significant as compared with 0.0005% latanoprost.

Discussion

In the present study, the intraocular pressure lowering effects of latanoprost and 15-keto-latanoprost in monkeys were compared following a single instillation at 0.0005%, for about one-tenth the amount of clinically used latanoprost. While no reduction in the intraocular pressure was noted following the instillation of 0.0005% latanoprost, the instillation of 0.0005% 15-keto-latanoprost significantly lowered the intraocular pressure.

Above results clearly indicate that the potency of intraocular pressure lowering effect of 15-keto-latanoprost is significantly greater than that of latanoprost. Furthermore, the fact that 15-keto-latanoprost exerted a significant intraocular pressure lowering effect at such a low concentration, at which latanoprost had no effect, strongly suggests that 15-keto acid of latanoprost, a 13,14-dihydro-15-keto-type metabolite produced from latanoprost in the eyes, participates in the intraocular pressure lowering effect after the instillation of latanoprost.

References

1) Sjöquist B., et al.: Drug metabolism and disposition 26 (8): 745-754, 1998

produced from latanoprost in the eye after instillation of latanoprost participates in the maintenance of the intraocular pressure lowering effect after instillation of latanoprost.

I. Introduction

In the present study, the animals were treated by the instillation with latanoprost at the clinical concentration alone, or additional instillation of a small amount of latanoprost or 15-keto-latanoprost 12 hours after instillation of latanoprost when the IOP showed the maximum reduction after instillation of latanoprost. The changes of IOP in 3 different treatment groups were compared to investigate the significance of the presence of 15-keto acid of latanoprost, a 13,14-dihydro-15-keto type metabolite, in maintaining the IOP lowering effect observed after instillation of latanoprost.

II. Materials and Methods

1. Test substance

15-keto-latanoprost and latanoprost which were synthesized in Ueno Institute for Medical Science were used.

2. Animals

Six male cynomolgus monkeys (body weight: 3.2 - 3.8 kg) were used. These monkeys were housed individually in cages for monkeys in a monkey rearing room which was maintained at room temperature of 24 ± 1°C, relative

observed after instillation of latanoprost.

The following 3 treatments were given to the right eye of monkeys at the intervals of at least 10 days. Namely, (1) instillation of 0.005% latanoprost alone, (2) additional instillation of 0.0005% latanoprost at 12 hours after instillation of 0.005% latanoprost, and (3) additional instillation of 0.0005% 15-keto-latanoprost at 12 hours after instillation of 0.005% latanoprost. Thirty μL of each test substance was instilled into the right eye of animals with a Pipetman (Gilson). The same amount of the vehicle was instilled into the left eye.

5. Measurement of IOP

After the ocular surface of monkeys was anesthetized with 0.4% oxybuprocaine hydrochloride (Benoxil® 0.4% solution, Santen Pharmaceutical Co., Ltd.) under i.m. systemic anesthesia with 5 - 7.5 mg/kg of ketamine hydrochloride, IOP was measured with an applanation pneumatonograph (Alcon Japan Ltd.). IOP was measured before instillation and at 4, 8, 12, 16, 20, 24, 28 and 32 hours after instillation of 0.005% latanoprost.

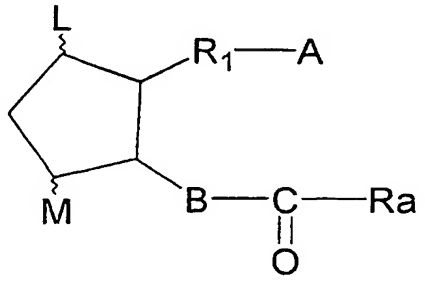
III. Results

As Fig. 4 shows, when 0.005% latanoprost alone was instilled into the eye of monkeys, IOP decreased with time at 4, 8 and 12 hours after instillation. The IOP returned with time toward the predosing levels at 16 and 20 hours

CLAIMS

1. An ophthalmic composition for reducing intraocular pressure or for treating glaucoma in a mammal, which comprises a 15-keto prostaglandin compound containing a ring structure at the end of the omega chain in a dose below the therapeutically effective dose of the corresponding 15-OH compound.

2. The composition of claim 1, wherein the 15-keto-prostaglaindin compound is represented by the formula (I),



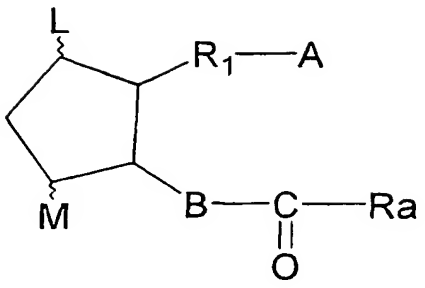
(I)

wherein L and M are hydrogen atom, hydroxy, halogen atom, lower alkyl, lower alkoxy, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-CH_2OH$, $-COCH_2OH$, -COOH or a functional derivative thereof;

B is $-CH_2-CH_2-$, -CH=CH- or $-C\equiv C-$;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is



(I)

Wherein L and M are hydrogen atom, hydroxy, halogen atom, lower alkyl, lower alkoxy, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-CH_2OH$, $-COCH_2OH$, $-COOH$ or a functional derivative thereof;

B is $-CH_2-CH_2-$, $-CH=CH-$ or $-C\equiv C-$;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, an alkyl group, hydroxy, oxo, aryl or heterocyclic group; and

Ra is a saturated or unsaturated lower aliphatic hydrocarbon residue, at the end of which is substituted with an aryl or aryloxy group.

9. The composition of claim 7, wherein the 15-keto prostaglandin compound is 13,14-dihydro-15-keto-18,19,20-trinor-PGF2α isopropyl ester.

10. The composition of claim 7, wherein the mammal is a human.

Ra is a saturated or unsaturated lower aliphatic hydrocarbon residue, at the end of which is substituted with an aryl or aryloxy group.

13. The method of claim 11, wherein the 15-keto prostaglandin compound is 13,14-dihydro-15-keto-18,19,20-trinor-PGF2α isopropyl ester.

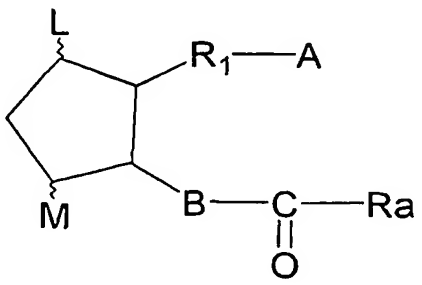
14. The method of claim11, wherein the dose is about one-tenth the therapeutically effective dose of the corresponding 15-OH compound.

15. The method of claim 13, wherein the dose is about 0.05 to below 5.0μg per eye.

16. The method of claim 11, wherein the mammal is a human.

17. A method for maintaining a reduced intraocular pressure in a mammal by periodically administrating to the eyes of the mammal an effective amount of a 15-keto prostaglandin compound containing a ring structure at the end of the omega chain.

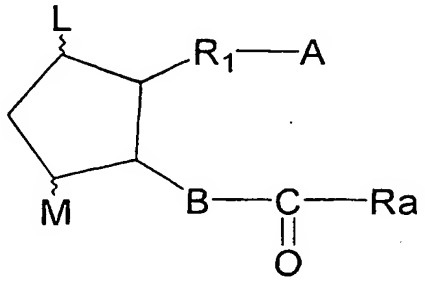
18. The method of claim 17, wherein the 15-keto-prostaglaindin compound is represented by the formula (I),



(I)

prostaglandin compound in a dose below the therapeutically effective dose of the corresponding 15-OH compound.

22. The use of claim 21, wherein the 15-keto-prostaglaindin compound is represented by the formula (I),



(I)

wherein L and M are hydrogen atom, hydroxy, halogen atom, lower alkyl, lower alkoxy, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-CH_2OH$, $-COCH_2OH$, -COOH or a functional derivative thereof;

B is $-CH_2-CH_2-$, -CH=CH- or $-C\equiv C-$;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, an alkyl group, hydroxy, oxo, aryl or heterocyclic group; and

Ra is a saturated or unsaturated lower aliphatic hydrocarbon residue, at the end of which is substituted with aryl, aryloxy.

23. The use of claim 21, wherein the 15-keto

hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-CH_2OH$, $-COCH_2OH$, -COOH or a functional derivative thereof;

B is $-CH_2-CH_2-$, -CH=CH- or $-C\equiv C-$;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, an alkyl group, hydroxy, oxo, aryl or heterocyclic group; and

Ra is a saturated or unsaturated lower aliphatic hydrocarbon residue, at the end of which is substituted with an aryl or aryloxy group.

29. The use of claim 27, wherein the 15-keto prostaglandin compound is 13,14-dihydro-15-keto-18,19,20-trinor-PGF2α isopropyl ester.

30. The use of claim 27, wherein the mammal is a human.

Fig. 3

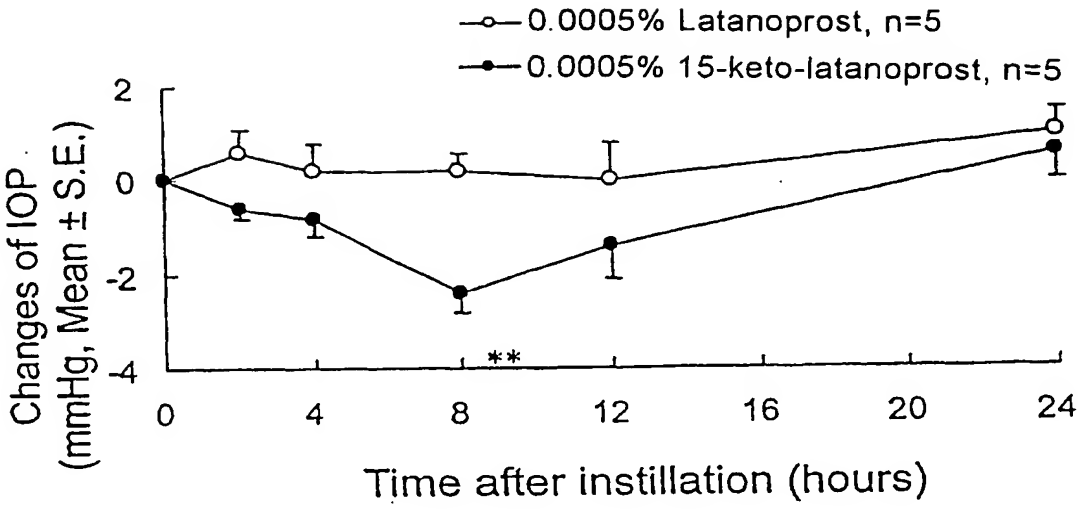
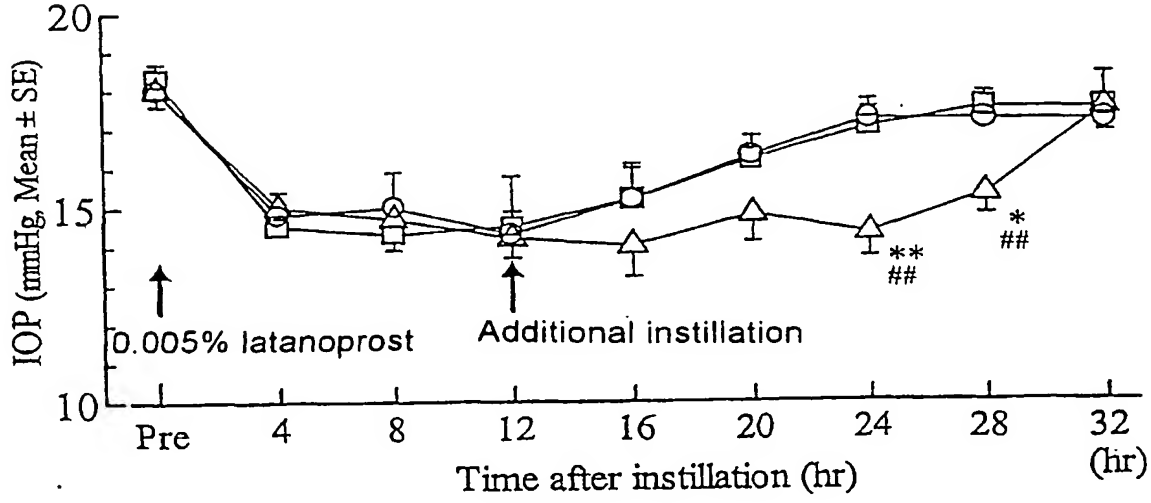

0.0005% Latanoprost, n=5
0.0005% 15-keto-latanoprost, n=5
Changes of IOP (mmHg, Mean ± S.E.)
2
0
-2
-4
**
0
4
8
12
16
20
24
Time after instillation (hours)

Fig. 4


IOP (mmHg, Mean ± SE)
20
15
10
0.005% latanoprost
Additional instillation
**
##
*
##
Pre
4
8
12
16
20
24
28
32
(hr)
Time after instillation (hr)

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/007731 A3

(54) Title: COMPOSITION CONTAINING A 15-KETO PROSTAGLANDIN COMPOUND FOR TREATING OF OCULAR HYPERTENSION AND GLAUCOMA

(57) Abstract: 15-keto prostaglandin compounds containing a ring structure at the end of the omega chain are used as ocular applied intraocular pressure reducing agents. They are applied in a dose below the known dose for the corresponding 15-OH compound.

International Application No
PCT/JP 01/06211

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 011 062 A (SCHNEIDER L WAYNE ET AL) 4 January 2000 (2000-01-04) abstract column 6, line 13 column 6, line 55 - line 65; claims	1-30
A	WO 99 51273 A (ALCON LAB INC) 14 October 1999 (1999-10-14) claims 1-5	1-30
A	EP 0 366 279 A (UENO SEIYAKU OYO KENKYUJO KK) 2 May 1990 (1990-05-02) abstract; claims; examples	1-30
A	EP 0 308 135 A (UENO SEIYAKU OYO KENKYUJO KK) 22 March 1989 (1989-03-22) abstract; claims; examples	1-30

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 01/06211

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 3,5,9,13,15,19,23,25,29
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 01/06211

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